Office Action Summary	Application No.	Applicant(s)	
	09/692,807	BUTROUS ET AL.	
	Examiner	Art Unit	
	Chris E. Simmons	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 06/22/2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

PREVIOUS REJECTIONS

35 U.S.C. § 103(a) Rejection of Claims 44-112 Over Ellis et al. (WO 94/28902)

Claims 44-112 were rejected under 35 U.S.C. 103(a) as being obvious over Ellis et l. (WO 94/28902). This rejection is maintained and is now applicable to newly added claims 113-118.

Applicants argue:

> Applicants respectfully submit that the Examiner is improperly and incorrectly interpreting Ellis et al. to teach a utility (pulmonary hypertension) for which there is **no basis for all the compounds disclosed therein**. **The only new utility taught by Ellis et al.** is that the compounds of formula I described in EP0463756 ("Bell I") and EP0526004 ("Bell II"), as well as other disclosed compounds, **are useful for the treatment of erectile dysfunction**. There is no new teaching that these compounds (the compounds disclosed in Bell I) are useful for treating pulmonary hypertension. **The only compounds disclosed as treating pulmonary hypertension are those compounds disclosed in Bell II." (Emphasis added)**

Examiner's response:

Applicants' arguments have been fully considered but they are not deemed to be persuasive. At issue, as Applicant points out, is the interpretation of a passage in disclosed in Ellis et al. The passage reads:

> "The **compounds of the invention** are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the **said compounds** in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA) , peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS)."

It is clear from this disclosure that Ellis et al. believe that the compounds of their invention (sildenafil is a specie) have already been disclosed in prior art to be useful in the treatment of, *inter alia*, pulmonary hypertension. In addition, this passage makes clear to the skilled artisan that the Ellis et al.'s compounds' selective enzyme inhibition leads to elevated cGMP levels which leads to the utilities already disclosed in the Bell references. The phrase, "said compounds", in the above passage has the antecedent basis clearly defined as being "the compounds of the invention**".** Ellis et al. discloses, not only common action, they also have a common core which strongly suggest a common group of utilities. This taken with the disclosure of dosages (i.e., 5-75 mg) that overlap the instantly claimed effective dosage range for the treatment of pulmonary hypertension. This provides the disclosure to the skilled artisan that pulmonary hypertension can be treated with amounts of sildenafil that will, naturally, selectively treat pulmonary hypertension over systemic hypertension.

Accordingly, there is clear basis for the interpretation previous set forth by the Examiner.

Applicant argues:

> "It is only by improper hindsight reconstruction that one of ordinary skill in the art would piece together the disclosures of three references: Bell I, Bell II and Ellis et al. to arrive at anything close to applicants' invention - a method of treating pulmonary hypertension by administrating sildenafil. Even so, such hindsight reconstruction leaves out the limitation that administration must be such that pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance."
>
> "As Applicants already discussed in previous responses, and as disclosed within Applicants' specification, for a compound to be useful in the long term treatment of chronic pulmonary hypertension, it preferably is selective for the pulmonary vascular system -not the systemic vascular system. If the compound is not selective and impacts the systemic vascular system, the patient would likely suffer adversely from cardiovascular hypotension. Applicants' invention is directed to a compound that preferentially acts on the pulmonary system, instead of the systemic system. Thus, the concern of cardiovascular hypertension is minimized."

Examiner's response:

As outlined above, Ellis et al. clearly provide the disclosure to the skilled artisan that pulmonary hypertension can be treated with amounts of sildenafil that will, naturally, selectively treat pulmonary hypertension over systemic hypertension.

NEW REJECTIONS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Note: The following rejection was necessitated by Applicant's submission of new prior art in the IDS submitted after the prior office action.

Claims 63-76, 94-98, 106-113, and 115-118 are rejected under 35 USC 103(a) as being unpatentable over Weimann et al. ("Sildenafil (Viagra) is a selective pulmonary vasodilator in acute pulmonary hypertension in awake sheep", American Journal of respiratory and Critical Care Medicine, Vol. 159 (3), pp. A163, Supplement S March (1999) in view of Ellis et al. (WO 94/28902).

Weimann et al. (provided in IDS) discloses sildenafil is a compound useful for treating pulmonary hypertension by administering it nasogastrically in an effective amount (i.e., 12.5, 25, and 50 mg) to treat pulmonary hypertension with little effect on systemic vascular resistance.

Weimann et al. does not expressly disclose the claimed amounts and etiologies of pulmonary hypertension, or subjects' age.

Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Accordingly, the combination of references renders the instantly claimed invention obvious.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to use the sildenafil compound to treat pulmonary hypertension.

It is not patentable to optimize dosage amounts of a composition through routine experimentation. Differences in dosage amounts from what is disclosed in the reference, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such dosage amounts are critical. It is not inventive to discover the optimum or workable ranges by routine experimentation. (See MPEP 2144.05 [R-5] II A). Furthermore, one of ordinary skill would alter the amounts of drug, whether the subject being treated is a child or adult.

The suggestion/motivation for doing so would have been optimize the effect of the compound by altering the dosage amounts while administering to a patient in a less invasive manner.

Therefore, it would have been obvious to combine the teachings in each reference to obtain the invention as specified in claims.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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